NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): DIAGNOSIS AND MANAGEMENT OF ACUTE EXACERBATIONS

GUIDELINES BEING COMPARED

1. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. [447 references]
2. **Singapore Ministry of Health (SMOH)**. Chronic obstructive pulmonary disease. Singapore: Singapore Ministry of Health; 2006 Oct. 84 p. [155 references]
3. **Department of Veterans Affairs, Department of Defense (VA/DoD)**. VA/DoD clinical practice guideline for management of outpatient chronic obstructive pulmonary disease. Washington (DC): Department of Veteran Affairs, Department of Defense; 2007. 138 p.

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AREAS OF AGREEMENT AND DIFFERENCE

A direct comparison of recommendations presented in the above guidelines for the diagnosis and management of acute exacerbation of COPD is provided below. The

VA/DoD guideline provides recommendations for the outpatient setting, while GOLD and SMOH address both hospital and outpatient settings.

Areas of Agreement

Diagnosis and Assessment of Severity

There is overall agreement that an exacerbation of COPD is generally defined as a worsening of the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations; is acute in onset; and may necessitate a change in regular medication. All groups recognize worsening dyspnea, increase in sputum purulence, and increase in sputum volume as cardinal symptoms of acute exacerbation. GOLD and VA/DoD agree that assessment of the severity of an exacerbation should be based upon medical history (including preexisting comorbidities), symptoms, physical examination, and laboratory investigations.

All of the groups recommend chest x-ray in the initial evaluation of patients with suspected acute exacerbation to identify alternative diagnoses that can mimic the symptoms of an exacerbation. GOLD also recommends ECG, which they state aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. VA/DoD also cites ECG as an appropriate investigation if clinically indicated. All of the groups agree that pulse oximetry can be used to evaluate oxygen saturation. GOLD and VA/DoD also recommend arterial blood gas analysis. With regard to spirometry, GOLD states that spirometric measurements are not accurate during an acute exacerbation and that their routine use is therefore not recommended. According to VA/DoD, spirometry can be considered in patients who are able to perform the test and for whom there are baseline data available for comparison. GOLD and VA/DoD agree that a complete blood count, which GOLD states may identify polycythemia (hematocrit > 55%) or bleeding, may be indicated. With regard to sputum culture, none of the groups recommends its routine use. GOLD states that if an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiogram should be performed. VA/DoD states that sputum culture may be indicated if pseudomonas is suspected (when there is underlying structural lung disease, chronic oral glucocorticoid use, recurrent antibiotic therapy, and malnutrition).

There is overall agreement that patients with possible COPD acute exacerbations should have differential diagnoses considered, assessed, and treated as necessary. The groups agree that common differential diagnoses include pneumonia, pneumothorax, CHF, pulmonary embolism, pleural effusion, recurrent aspiration, cardiac arrhythmia, upper airway obstruction, and symptoms resulting from noncompliance with medications.

Oxygen Therapy

The two guidelines to address oxygen therapy, GOLD and SMOH, agree that it is beneficial for patients with acute exacerbation and hypoxemia. GOLD states that oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. GOLD also recommends monitoring of arterial blood gases to ensure satisfactory oxygenation without CO_2 retention or acidosis. SMOH recommends that the lowest possible oxygen concentration to maintain oxygen saturation above 90% be provided. With regard to method of administration, SMOH states that oxygen can

be administered via nasal prongs or venturi mask. According to GOLD, venturi masks offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient. The VA/DoD addresses outpatient management of COPD, and so therefore does not provide recommendations regarding oxygen therapy in hospital, but they do, however, recommend early initiation of oxygen for patients being admitted to the ED.

Mechanical Ventilation

The two guidelines to address inpatient management of acute exacerbations, GOLD and SMOH, agree that NIV is a beneficial therapeutic option for management of respiratory failure in patients in hospital. According to GOLD, NIV improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces $PaCO_2$, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality. SMOH states that NIV should be used as the treatment of choice in the hospital for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. GOLD provides indications and relative contraindications for NIV, as well as indications for the use of invasive mechanical ventilation.

Outpatient/Home vs. Inpatient Management

The groups agree that more severe exacerbation or inadequate resources in the outpatient setting may require evaluation and management of the patient in the ED or a hospital setting. Indications for referral to the ED cited by the groups include, but are not limited to, changes in mental status (e.g., confusion), inadequate disease management resources at home, new or worsening hypoxemia, onset of new physical signs (e.g., cyanosis), severe dyspnea, and unstable vital signs. GOLD and VA/DoD agree that initiation of bronchodilator therapy and oxygen is appropriate prior to full assessment and treatment in the ED.

Bronchodilator Therapy

The groups agree that nebulizers and metered dose inhalers are equally effective in achieving bronchodilation in COPD exacerbations. The guidelines further agree that methylxanthines (theophylline, aminophylline) should not be routinely recommended in patients with acute exacerbation of COPD because of their adverse effects and the lack of proven therapeutic efficacy for this indication. GOLD, in the context of inpatient management of exacerbations, notes however, that methylxanthines are currently considered second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators. Refer to Areas of Difference for additional information.

Glucocorticosteroids

All of the groups agree that oral glucocorticosteroids are beneficial in the outpatient management of patients with acute exacerbation. The two groups to address inpatient management, GOLD and SMOH, agree that corticosteroids are beneficial in this setting as well. All three groups recommend a course of 30-40 mg daily of oral prednisolone for the treatment of acute exacerbations, but for different durations: 7 to 10 days (GOLD), 7 to 14 days (SMOH), and up to 14 days (VA/DoD).

Antibiotics

There is general agreement among the guidelines that antibiotics are beneficial in patients with at least two of the three cardinal symptoms of severe exacerbation (i.e., increased dyspnea, increased sputum volume, and increased sputum purulence). When choosing an antibiotic, GOLD and VA/DoD recommend stratifying patients according to the severity of the exacerbation. For mild exacerbations with no risk factors for poor outcomes, GOLD recommends oral treatment with a beta-lactam, a tetracycline, or TMP/SMX. For moderate exacerbations with risk factor(s) for poor outcome, they recommend a beta-lactam/beta-lactamase inhibitor, and for severe exacerbation with risk factors for *P. aeruginosa* infection, a fluoroquinolone. GOLD also provides recommendations for alternative oral regimens (particularly for areas with high incidence of *S. pneumoniae* resistant to penicillin) and parental/inpatient treatment.

VA/DoD similarly notes that stratifying the patient as complicated or uncomplicated may be helpful in determining the choice of antibiotic and recommends considering doxycycline, TMP/SMX, or a second generation cephalosporin for uncomplicated exacerbations of COPD. For complicated exacerbations, VA/DoD recommends a beta-lactam/beta-lactamase inhibitor or a fluoroquinolone. According to VA/DoD, choice of antibiotic agents may be determined based on the frequency of exacerbations in the past 12 months, severity of underlying COPD, presence of cardiac disease, and recent (within 3 months) antibiotic exposure for each patient. See Areas of Difference for additional information.

Areas of Difference

Bronchodilator Therapy

GOLD recommends short-acting beta$_2$-agonists as initial pharmacologic management of acute exacerbations, followed by the addition of an inhaled anticholinergic if a patient fails to respond to initial single-agent therapy. GOLD acknowledges that the evidence for the effectiveness of this combination remains controversial. SMOH, in contrast, states that both inhaled anticholinergic bronchodilators and inhaled short-acting beta$_2$-agonists are beneficial in the treatment of acute exacerbation of COPD, and that anticholinergic bronchodilators should be considered first because they have fewer and more benign side effects. VA/DoD does not cite one short-acting bronchodilator over another, recommending either a short-acting anticholinergic or short-acting beta$_2$-agonist (or a combination of both). They state that the choice of agent should be made on the basis of individual assessment and initial response to therapy.

Antibiotics

GOLD and VA/DoD recommend choosing an antibiotic based on severity of the exacerbation and other risk factors, with both recommending a tetracycline, TMP/SMX, or a beta-lactam (VA/DoD specifies a second generation cephalosporin) for less severe exacerbations, and reserving beta-lactam/beta-lactamase inhibitors and fluoroquinolones for more complicated/severe exacerbations. SMOH, in contrast, states that initial empirical treatment can be a beta-lactam/beta-lactamase inhibitor combination, a second generation macrolide, a second generation cephalosporin, or a quinolone.

COMPARISON OF RECOMMENDATIONS	
DIAGNOSIS AND INITIAL ASSESSMENT **Abbreviations** **Back to TOC**	
GOLD (2009)	**Key Points** • An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD. **Diagnosis and Assessment of Severity** **Medical History** Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as tachycardia and tachypnea, malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does prior history of chronic sputum production. **Assessment of Severity** Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests (see Figure 5.4-1 in the original guideline document). Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities. When available, prior arterial blood gas measurements are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. Thus, where possible, physicians should instruct their patients to bring the summary of their last evaluation when they come to the hospital with an exacerbation. In patients with Stage IV: Very Severe COPD, the most important sign of a severe exacerbation is a change in the mental status of the patient and

this signals a need for immediate evaluation in the hospital.

Spirometry and PEF. Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended.

Pulse oximetry and arterial blood gas measurement. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. For patients that require hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A PaO_2 < 8.0 kPa (60 mm Hg) and/or SaO_2 < 90% with or without $PaCO_2$ > 6.7 kPa (50 mmHg) when breathing room air indicate respiratory failure. In addition, moderate-to-severe acidosis (pH < 7.36) plus hypercapnia ($PaCO_2$ > 6 to 8 kPa, 45 to 60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation.

Chest X-ray and ECG. Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. Although the history and physical signs can be confusing, especially when pulmonary hyperinflation masks coexisting cardiac signs, most problems are resolved by the chest X-ray and ECG. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in advanced COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

Other laboratory tests. The whole blood count may identify polycythemia (hematocrit > 55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting empirical antibiotic treatment. *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Bio-chemical test abnormalities can be associated with an exacerbation and include electrolyte disturbance(s) (e.g., hyponatremia, hypokalemia), poor glucose control, or metabolic acid-base disorder. These abnormalities can also be due to associated co-morbid conditions.

Differential Diagnoses

	A diagnosis of pulmonary embolism should be considered in patients with exacerbation severe enough to warrant hospitalization, especially in those with an intermediate-to-high pretest probability of pulmonary embolism. Ten to 30% of patients with apparent exacerbations of COPD do not respond to treatment. In such cases the patient should be re-evaluated for other medical conditions that can aggravate symptoms or mimic COPD exacerbations. These conditions include pneumonia, CHF, pneumothorax, pleural effusion, pulmonary embolism, and cardiac arrhythmia. Noncompliance with the prescribed medication regimen can also cause increased symptoms that may be confused with a true exacerbation. Elevated serum levels of brain-type natriuretic peptide, in conjunction with other clinical information, identifies patients with acute dyspnea secondary to CHF and enables them to be distinguished from patients with COPD exacerbations.
SMOH (2006)	**Definition of an Acute Exacerbation** There is no widely accepted definition of acute exacerbation of COPD. Most published definitions describe an exacerbation as an acute event with worsening of the patient's symptoms from their usual stable state, which is beyond normal day-to-day variations. Commonly reported symptoms are worsening breathlessness, cough, increased sputum volume and sputum purulence. An acute exacerbation of COPD is a clinical diagnosis. **Differential Diagnoses of Acute Exacerbations** • Pneumonia • Pneumothorax • Left ventricular failure/pulmonary oedema • Pulmonary embolism • Lung cancer • Upper airway obstruction • Pleural effusion • Recurrent aspiration **Investigations for Patients with Exacerbation** **C** - Chest radiography is recommended in an acute exacerbation, when other diagnoses like pneumonia or heart failure need to be excluded. (**Grade C, Level 2+**) **D** - Sputum culture is not recommended for routine investigation of patients with exacerbation. (**Grade D, Level 3**) **D** - Pulse oximetry, if available, can assist doctors in identifying patients with hypoxaemia when oxygen saturation (SaO_2) is less

	than 90%. (**Grade D, Level 3**) Refer to page 51 of the original guideline document for an algorithm for the management of an acute exacerbation.
VA/DoD (2007)	**Definition of Acute Exacerbation** An exacerbation is a sustained worsening of the patient's respiratory symptoms and function from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worse breathlessness, cough, increased sputum production, and change in sputum color. The change in the patient's condition often necessitates a change in medication. **Assessment of Acute Exacerbation in the ED** In the ED, patients experiencing an acute exacerbation of COPD should be evaluated for the potential factors that contribute to the exacerbation. Assessment and treatment should proceed simultaneously in these patients. The ED should have the ability to perform these evaluations and treatments in a timely fashion. Increased respiratory symptoms in COPD can be due to a number of cardiac or pulmonary causes. Appropriate management mandates knowledge of the cause while simultaneously treating the severely ill patient. All patients with possible COPD acute exacerbations who either present directly to the ED or who are referred from outpatient settings should have the following differential diagnoses considered, assessed, and treated as necessary: • CHF • Pneumonia • Pneumothorax • Pulmonary embolism • Cardiac ischemia • Cardiac arrhythmia • Upper airway infection; e.g., acute sinusitis • Upper airway obstruction • Pleural effusion • Recurrent aspiration • Noncompliance with medications • Inappropriate oxygen therapy which may produce hypercapnia • Adverse effects of medications; e.g., sedatives. Clinical evaluation and diagnostic workup for patients admitted to the ED for acute exacerbation of COPD will cover the following: a. Clinical evaluation:

- Vital signs including oximetry
- Mental status
- Clinical evidence of impending respiratory failure (tachypnea, accessory muscle use, abdominal paradox, and cyanosis)
- Clinical signs and symptoms (e.g., cardiovascular disease, pulmonary embolism)

b. Diagnostic testing may include:
- Chest X-ray
- Arterial blood gases
- Complete blood count and differential
- BUN, creatinine, and electrolytes
- ECG
- Theophylline level, if patient is on theophylline
- Sputum cultures if pseudomonas is suspected (when there is underlying structural lung disease, chronic oral glucocorticoid use, recurrent antibiotic therapy, and malnutrition)

c. Patients in acute respiratory distress should receive nebulized bronchodilator therapy, systemic glucocorticoids, and antibiotics and oxygen, if indicated, while simultaneously being assessed for the need for non-invasive or invasive ventilation.

Management of Acute Exacerbation in the Outpatient Setting

Assessment, Testing, and Diagnosis

Action Statement

Patients with COPD with acute exacerbation should be assessed to confirm the diagnosis, rule out other causes for worsening symptoms and determine the severity of the exacerbation, and the priorities for treatment.

Recommendations

- The diagnosis of acute exacerbation of COPD should be confirmed and other causes excluded based upon clinical evaluation with additional diagnostic tests in selected cases. [I]
- The severity of an exacerbation of COPD should be determined based upon medical history, symptoms, physical examination, and pulmonary function tests. [I]
- Medical history with a patient with acute exacerbation should include:
  a. Onset, duration, and type of symptoms (cough, sputum production, dyspnea, fever, decreased exercise tolerance, confusion, or acute mental status changes)
  b. Current medication use
  c. History of prior COPD exacerbations or hospitalizations (frequency, ICU admissions, and prior intubation)
  d. The severity of the underlying COPD

	e. Presence of comorbid conditions; e.g., heart disease • Physical examination with a patient with acute exacerbation should include: a. Vital signs b. Level of consciousness c. A careful pulmonary examination d. Cardiovascular examination e. Oxygenation • Laboratory testing that may be considered with a patient with acute exacerbation: a. Oximetry (in all patients with moderate or worse COPD) b. Arterial blood gas in patients with deteriorating clinical status c. Spirometry, if available, in patients who are able to perform the test and for whom there is baseline data available for comparison d. Chest X-ray to exclude other causes if clinically suspected e. ECG if clinically indicated • Alternative causes of increased symptoms that need to be clinically excluded include: a. CHF b. Pneumonia c. Pneumothorax d. Pulmonary embolism e. Cardiac ischemia f. Cardiac arrhythmia g. Upper airway infection; e.g., acute sinusitis h. Upper airway obstruction i. Pleural effusion j. Recurrent aspiration k. Noncompliance with medications l. Inappropriate oxygen therapy m. Adverse effects of medications; e.g., sedatives
MANAGEMENT **Abbreviations** **Back to TOC**	
Emergency Referral	
GOLD (2009)	**Home Management** There is increasing interest in home care for end-stage COPD patients, although economic studies of home care services have yielded mixed results. Four randomized clinical trials have shown

that nurse-administered home care (also known as "hospital-at-home" care) represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure. However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting.

The algorithm reported in Figure 5.4-2 in the original guideline document may assist in the management of an exacerbation at home; a stepwise therapeutic approach is recommended.

Hospital Management

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success, but returning them to their homes with increased social support and a supervised medical care package after initial emergency room assessment has been much more successful. Savings on inpatient expenditures offset the additional costs of maintaining a community-based COPD nursing team. However, detailed cost-benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown below. Some patients need immediate admission to an intensive care unit (ICU) (see below). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Indications for Hospital Assessment or Admission for Exacerbations of COPD

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age

	• Insufficient home support **Indications for ICU Admission of Patients with Exacerbations of COPD** • Severe dyspnea that responds inadequately to initial emergency therapy • Changes in mental status (confusion, lethargy, coma) • Persistent or worsening hypoxemia (PaO_2 <5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia ($PaCO_2$ >8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive ventilation • Need for invasive mechanical ventilation • Hemodynamic instability — need for vasopressors **ED or Hospital** The first actions when a patient reaches the ED are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening (see above). If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the ED or hospital as detailed in Figure 5.4-5 in the original guideline document.
SMOH (2006)	**When to Refer to the ED** **GPP** - Any one of the following signs may indicate severe exacerbations requiring urgent referral to the ED: 1. Marked dyspnoea and tachypnoea (> 30 respirations/minute) 2. Use of accessory muscles (sternomastoid and abdominal) at rest 3. Cyanosis 4. Confusion 5. SaO_2 <90% **(GPP)**
VA/DoD (2007)	**<u>Referral to the ED</u>** **Criteria for Referring to the ED/Hospital** Most patients with an exacerbation of COPD can be evaluated in an outpatient clinic setting and managed at home. However, certain conditions may require referral of the patient to a higher care facility (ED/hospital).

Action Statement

More severe exacerbation or inadequate resources in the outpatient setting may require evaluation and management of the patient in the ED or a hospital setting. [I]

Recommendations

- Patients evaluated for acute exacerbation of COPD should be considered for referral to the ED or admission to the hospital if they present with any of the following indications [I]:
    a. Unstable vital signs
    b. Impaired level of consciousness or altered mental status
    c. Severe breathlessness
    d. New or worsening hypoxemia (SaO_2 < 90 percent)
    e. Inadequate disease management resources at home
    f. Lack of appropriate resources to evaluate or manage the patient in a clinic setting

Initiation of Short-Acting Bronchodilator and/or Oxygen Therapy if Necessary

Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed with increased doses of short-acting bronchodilators. Hypoxemia can develop or worsen with an exacerbation and can be life-threatening. This hypoxemia can be readily alleviated with low flow oxygen. Patients referred for further evaluation and management to an ED or hospital should receive these therapies promptly, if available.

Action Statement

Early initiation of bronchodilator therapy and oxygen (in hypoxemic patients) is appropriate prior to full assessment and treatment in the ED or hospital.

Recommendations

- Initial treatment for patients experiencing an initial acute exacerbation of COPD who have been referred to the ED or admitted directly to the hospital should include [I]:
    a. Short-acting bronchodilator, by nebulizer or metered dose inhaler, if readily available
    b. Low flow oxygen therapy to maintain SaO_2 at 90 percent

Bronchodilators

GOLD (2009)	**Key Points**: • Inhaled bronchodilators (particularly inhaled beta$_2$-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (**Evidence A**). **<u>Home Management</u>** **Bronchodilator Therapy** Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a beta$_2$-agonist (**Evidence A**). There is not sufficient evidence, however, to indicate a difference in efficacy between the different classes of short-acting bronchodilators, or to indicate additional benefit of combinations of short-acting bronchodilators. However, if not already used, an anticholinergic can be added until the symptoms improve. There is no difference in the clinical response between bronchodilator therapy delivered by metered-dose inhaler with a spacer and by hand held nebulizer. **<u>Hospital Management</u>** **Bronchodilator Therapy** Short-acting inhaled beta$_2$-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD (**Evidence A**). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its wide-spread clinical use, the role of methylxanthines in the treatment of exacerbations of COPD remains controversial. Methylxanthines (theophylline or aminophylline) are currently considered second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators (**Evidence B**). Possible beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent, whereas adverse effects are significantly increased. There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either beta$_2$-agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.
SMOH (2006)	**A** - Inhaled anticholinergic bronchodilators or inhaled short-acting beta$_2$-agonists are beneficial and should be used in the treatment of patients presenting with acute exacerbation of COPD. (**Grade A, Level 1+**) Since the inhaled anticholinergic bronchodilators have fewer and

	more benign side effects, consider these agents first. Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial. **D** - Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD, as they are equally effective in achieving bronchodilation in COPD exacerbations. (**Grade D, Level 4**) The choice of delivery system should depend on the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy.
VA/DoD (2007)	**Pharmacotherapy for Acute Exacerbation in Outpatient Settings** **Bronchodilators** Pharmacotherapy should be initiated in the acute exacerbation to hasten resolution of the signs/symptoms of the exacerbation and prevent complications. This treatment may include antibiotics, systemic glucocorticoids, and bronchodilators. Patients who present with acute exacerbations of COPD need immediate relief of dyspnea. The approach is to provide inhaled short-acting bronchodilators delivered either by a metered dose inhaler or aerosol nebulization. These are provided until the patient's dyspnea is sufficiently reduced, which may take as few as one treatment or many treatments over a number of hours or days. Action Statement Provide relief of symptoms and improve FEV_1 with short-acting inhaled bronchodilator therapy. [B] Recommendations • A short-acting bronchodilator (short-acting anticholinergic or short-acting $beta_2$-agonist) or a combination of both, using a metered dose inhaler with a spacer or aerosol mobilization, should be administered as soon as possible and as frequently as necessary. The choice of agent should be made on the basis of individual assessment and initial response to therapy. [B] • Methylxanthines should be avoided either orally or systemically since these agents may lead to side effects and have no proven efficacy in the setting of an acute exacerbation of COPD. [D]
Corticosteroids	

GOLD (2009)	**Key Points**: • Inhaled bronchodilators (particularly inhaled beta$_2$-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (**Evidence A**). **<u>Home Management</u>** **Glucocorticosteroids** Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV_1) and hypoxemia (PaO_2) (**Evidence A**), and may reduce the risk of early relapse, treatment failure, and length of hospital stay. They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% predicted. A dose of 30 to 40 mg prednisolone per day for 7 to 10 days is recommended. Therapy with oral prednisolone is preferable. Budesonide alone, or in combination with formoterol, may be an alternative (although more expensive) to oral glucocorticosteroids in the treatment of exacerbations and is associated with significant reduction of complications. **<u>Hospital Management</u>** **Glucocorticosteroids** Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD (**Evidence A**). The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. 30 to 40 mg of oral prednisolone daily for 7 to 10 days is effective and safe (**Evidence C**). Prolonged treatment does not result in greater efficacy and increases the risk of side effects (e.g., hyperglycemia, muscle atrophy).
SMOH (2006)	**Systemic Corticosteroids** **A** - In the absence of significant contraindications, oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD. (**Grade A, Level 1+**) **A** - In the absence of significant contraindications, oral corticosteroids should be considered in patients managed in the community who have an exacerbation with a significant increase in the breathlessness which interferes with daily activities. (**Grade A, Level 1+**)

	A - Prednisolone 30 mg orally should be prescribed for 7 to 14 days to patients with an exacerbation. It is recommended that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy. (**Grade A, Level 1+**)
VA/DoD (2007)	**<u>Pharmacotherapy for Acute Exacerbation in Outpatient Settings</u>** **Oral Glucocorticoids** <u>Action Statement</u> Consider a course of oral glucocorticoids in the treatment of an acute exacerbation of COPD to improve outcomes. [A] <u>Recommendations</u> A short course of oral glucocorticoids with a dose equivalent to 30 to 40 mg of prednisone per day (up to 14 days) should be considered for patients with COPD exacerbation. [A]
Antibiotics	
GOLD (2009)	**Key Points**: • Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotic treatment (**Evidence B**). **<u>Hospital Management</u>** **Antibiotics** Based on the current available evidence, antibiotics should be given to: • Patients with exacerbations of COPD with three of the following cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence (**Evidence B**) • Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (**Evidence C**) • Patients with a severe exacerbation of COPD that requires invasive mechanical ventilation (invasive or noninvasive) (**Evidence B**) Figure 5.4-7 in the original guideline document provides recommended antibiotic treatment for exacerbations of COPD, although it must be emphasized that most of the published studies

	related to the use of antibiotics were done in chronic bronchitis patients. The route of administration (oral or intravenous) depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred; if the IV route must be used, switching to the oral route is recommended when clinical stabilization permits. Based on studies of the length of use of antibiotics for chronic bronchitis, antibiotic treatment in patients with COPD exacerbations could be given for 3 to 7 days (**Evidence D**).
SMOH (2006)	**A** - Antibiotics should be used to treat exacerbations of COPD when (Saint et al. 1995): 1. There is history of purulent sputum 2. There are clinical signs of pneumonia 3. There is consolidation on a chest radiograph **(Grade A, Level 1+)** Initial empirical treatment can be a beta lactam-beta lactamase inhibitor combination, a 2nd generation macrolide, a 2nd generation cephalosporin, or a quinolone. When initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists.

VA/DoD (2007)	**<u>Pharmacotherapy for Acute Exacerbation in Outpatient Settings</u>**
	
	Antibiotics
	
	<u>Action Statement</u>
	
	Prescribe a course of antibiotics for acute exacerbation of COPD if symptoms indicate bacterial infection; choice of antibiotic agent may be based on the degree of complication (number of exacerbations, FEV_1, previous exposure to antibiotics, and cardiac disease).
	
	<u>Recommendations</u>
	
	• COPD patients with acute exacerbation of COPD with at least two of the following will most likely benefit from antibiotic therapy [A]:
	  a. Increased sputum purulence (change in sputum color)
	  b. Increased sputum volume
	  c. Increased dyspnea
	• Choice of antibiotic agents may be determined based on local bacterial resistance patterns. [C]
	• Choice of antibiotic agents may be determined based on the frequency of exacerbations in the past 12 months, severity of

	underlying COPD, presence of cardiac disease, and recent (within 3 months) antibiotic exposure for each patient. [B] • For uncomplicated exacerbations of COPD, consider doxycycline, TMP/SMX, second generation cephalosporin. [C] • For complicated exacerbations of COPD, consider beta-lactam/beta-lactamase inhibitor or fluoroquinolone. [C] Stratifying the patient as complicated or uncomplicated may be helpful in determining the choice of antibiotic and is summarized in Table 13 of the original guideline document.
Oxygen Therapy	
GOLD (2009)	**<u>Hospital Management</u>** **Controlled Oxygen Therapy** Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 >8.0 kPa, 60 mm Hg, or SaO_2 >90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 to 60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient.
SMOH (2006)	**GPP** - Oxygen therapy should be considered if patient is known, or suspected, to have hypoxaemia. This can be administered via nasal prongs, or venturi mask. One should exercise caution in the oxygen dose for patients, such that the lowest possible oxygen concentration to maintain oxygen saturation above 90% is provided. If pulse oximetry is not available, the concentration of the oxygen mask should not exceed 28%, or the nasal prong oxygen flow rate should be kept at 2L/min. **(GPP)**
VA/DoD (2007)	**Initiation of Short-Acting Bronchodilator and/or Oxygen Therapy if Necessary** Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed with increased doses of short-acting bronchodilators. Hypoxemia can develop or worsen with an exacerbation and can be life-threatening. This hypoxemia can be readily alleviated with low flow oxygen. Patients referred for further evaluation and management to an ED or hospital should receive these therapies promptly, if available.

	Action Statement Early initiation of bronchodilator therapy and oxygen (in hypoxemic patients) is appropriate prior to full assessment and treatment in the ED or hospital. Recommendations • Initial treatment for patients experiencing an initial acute exacerbation of COPD who have been referred to the ED or admitted directly to the hospital should include [I]: a. Short-acting bronchodilator, by nebulizer or metered dose inhaler, if readily available b. Low flow oxygen therapy to maintain SaO_2 at 90 percent
Noninvasive and Invasive Ventilation	
GOLD (2009)	**Key Points**: • Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces $PaCO_2$, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality (**Evidence A**). **Hospital Management** **Ventilatory Support** The primary objectives of mechanical ventilator support in patients with COPD exacerbations are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive intermittent ventilation using either negative or positive pressure devices, and invasive (conventional) mechanical ventilation by oro-tracheal tube or tracheostomy. **Noninvasive Mechanical Ventilation** NIV has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80 to 85%. These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases $PaCO_2$), decreases respiratory rate, severity of breathlessness, and length of hospital stay (**Evidence A**). More importantly, mortality — or its surrogate, intubation rate — is reduced by this intervention. However, NIV is not appropriate for all patients, as

summarized below.

Indications and Relative Contraindications for NIV

Selection Criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH < 7.35) and/or hypercapnia ($PaCO_2$ >6.0 kPa, 45 mmHg)
- Respiratory frequency > 25 breaths per minute

Exclusion Criteria (any may be present)

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Change in mental status; uncooperative patient
- High aspiration risk
- Viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma
- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity

Invasive Mechanical Ventilation

During exacerbations of COPD the events occurring within the lungs include bronchoconstriction, airway inflammation, increased mucus secretion, and loss of elastic recoil, all of which prevent the respiratory system from reaching its passive functional residual capacity at the end of expiration, enhancing dynamic hyperinflation and increasing the work of breathing. The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown below, including failure of an initial trial of NIV. As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV. Figure 5.4-10 in the original guideline document details some other factors that determine the use of invasive ventilation.

The use of invasive ventilation in end-stage COPD patients is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. When possible, a clear statement of the patient's own treatment wishes — an advance directive or "living will" — makes these difficult decisions much easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to

	wean to spontaneous ventilation. **Indications for Invasive Mechanical Ventilation** • Unable to tolerate NIV or NIV failure (for exclusion criteria, see above) • Severe dyspnea with use of accessory muscles and paradoxical abdominal motion • Respiratory frequency >35 breaths per minute • Life-threatening hypoxemia • Severe acidosis (pH <7.25) and/or hypercapnia ($PaCO_2$ >8.0 kPa, 60 mmHg) • Respiratory arrest • Somnolence, impaired mental status • Cardiovascular complications (hypotension, shock) • Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion) **Factors Determining the Decision to Initiate Invasive Mechanical Ventilation** • Cultural attitudes toward chronic disability • Expectations of therapy • Financial resources (especially the provision of ICU facilities) • Perceived likelihood of recovery • Customary medical practice • Wishes, if known, of the patient Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load. By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD. Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate. In COPD patients that failed extubation, noninvasive ventilation facilitates weaning and prevents reintubation, but does not reduce mortality. A report that included COPD and non-COPD patients showed that noninvasive mechanical ventilation in patients that failed extubation was not effective in averting the need for reintubation and did not reduce mortality.
SMOH (2006)	**A** - Non-invasive ventilation should be used as the treatment of choice in the hospital, for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. (**Grade A, Level 1+**) **Note**: Refer to the original guideline document for a discussion of air travel in COPD

	patients.
VA/DoD (2007)	No recommendations offered.

HOSPITAL DISCHARGE AND FOLLOW-UP
Abbreviations
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GOLD (2009)	**Key Points**: • Medications and education to help prevent future exacerbations should be considered as part of follow-up, as exacerbations affect the quality of life and prognosis of patients with COPD. **Hospital Discharge and Follow-Up** Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients developing an exacerbation of COPD although units with more respiratory consultants and better quality organized care have lower mortality and reduced length of hospital stay following admission for acute COPD exacerbation. Consensus and limited data support the discharge criteria listed below. Also provided below are items to include in a follow-up assessment 4 to 6 weeks after discharge from the hospital. Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters. Prior hospital admission, oral glucocorticosteroids, use of LTOT, poor health related quality of life, and lack of routine physical activity have been found to be predictive of readmission. Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rates. Use of a written action plan in COPD increased appropriate therapeutic interventions for exacerbations of COPD, an effect that does not decrease health-care resource utilization (**Evidence B**). In patients hypoxemic during a COPD exacerbation, arterial blood gases and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3 months. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required. Opportunities for prevention of future exacerbations should be reviewed before discharge, with particular attention to smoking cessation, current vaccination (influenza, pneumococcal vaccines), knowledge of current therapy including inhaler technique, and how to recognize symptoms of exacerbations.

	Pharmacotherapy known to reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization, such as long-acting inhaled bronchodilators, inhaled glucocorticosteroids, and combination inhalers, should be specifically considered. Early outpatient pulmonary rehabilitation after hospitalization for a COPD exacerbation is safe and results in clinically significant improvements in exercise capacity and health status at 3 months. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability. **Discharge Criteria for Patients with Exacerbations of COPD** • Inhaled $beta_2$-agonist therapy is required no more frequently than every 4 hours. • Patient, if previously ambulatory, is able to walk across room. • Patient is able to eat and sleep without frequent awakening by dyspnea. • Patient has been clinically stable for 12 to 24 hours. • Arterial blood gases have been stable for 12 to 24 hours. • Patient (or home caregiver) fully understands correct use of medications. • Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions). • Patient, family, and physician are confident patient can manage successfully at home. **Items to Assess at Follow-Up Visit 4 to 6 Weeks After Discharge from Hospital for Exacerbations of COPD** • Ability to cope in usual environment • Measurement of FEV_1 • Reassessment of inhaler technique • Understanding of recommended treatment regimen • Need for LTOT and/or home nebulizer (for patients with *Stage IV: Very Severe COPD*)
SMOH (2006)	No recommendations offered.
VA/DoD (2007)	**<u>Follow-Up</u>** **Recommendations** Patients should be instructed that if they have not improved with therapy over 48 to 72 hours or if they deteriorate at any time, they should seek attention from a healthcare provider. [I]

STRENGTH OF EVIDENCE AND RECOMMENDATION GRADING SCHEMES Abbreviations Back to TOC	
GOLD (2009)	**Description of Levels of Evidence** A. *Sources of Evidence*: Randomized controlled trials (RCTs). Rich body of data. *Definition*: Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. B. *Sources of Evidence*: Randomized controlled trials. Limited body of data. *Definition*: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. C. *Sources of Evidence*: Nonrandomized trials. Observational studies. *Definition*: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies. D. *Sources of Evidence*: Panel consensus. Judgment. *Definition*: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.
SMOH (2006)	**Levels of Evidence** **Level 1++**: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias. **Level 1+**: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. **Level 1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias **Level 2++**: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

	Level 2+: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **Level 2-**: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **Level 3**: Non-analytic studies (e.g. case reports, case series) **Level 4**: Expert opinion **Grades of Recommendation** **Grade A**: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **Grade B**: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ **Grade C**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ **Grade D**: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **GPP** (good practice points): Recommended best practice based on the clinical experience of the guideline development group.
VA/DoD (2007)	**Quality of Evidence** **I** — At least one properly done randomized controlled trial (RCT) **II-1** — Well designed controlled trial without randomization **II-** — Well designed cohort or case-control analytic study

2	
II-3	Multiple time series, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, case reports, and expert committees

Overall Quality

Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; or moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Net Effect of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering or A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering or A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering or A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients or No relative impact on either a frequent condition with a substantial burden of suffering; or an infrequent condition with a significant impact on the individual patient level.

Strength of Recommendation

	Net Benefit of the Intervention

Quality of Evidence	Substantial	Moderate	Small	Zero or Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Evidence Rating System

A	A strong recommendation that the clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

Where existing literature was ambiguous or conflicting, or where scientific data were lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus" and given the grade **[I]**.

COMPARISON OF METHODOLOGY *Click on the links below for details of guideline development methodology*		
GOLD (2009)	**SMOH (2006)**	**VA/DoD (2007)**
All of the groups performed searches of electronic databases to collect/select the evidence; GOLD also performed hand-searches of published literature (primary and secondary sources). The two groups to describe this process, GOLD and VA/DoD, provide relevant details including the names of databases searched, date ranges searched, and inclusion criteria applied. To assess the quality and strength of the evidence all three groups weighted it according to a rating scheme and provide the scheme. Methods used to analyze the evidence were similar as well, with all of the groups having performed a review of published meta-analyses as well as a systematic review. The GOLD and VA/DoD systematic reviews incorporated evidence tables. VA/DoD provides a description of the evidence analysis process; GOLD and SMOH do not. Expert consensus was employed by all three groups to formulate the recommendations, and all of the groups, with the exception of GOLD, rated the strength of the recommendations according to a scheme. All of the groups except SMOH provide details regarding the recommendation formulation process. While none of the groups performed a cost analysis, GOLD and SMOH reviewed published cost analyses and discuss the findings. With regard to methods used to validate the guideline, GOLD and VA/DoD sought both internal and external peer review and provide a description of the processes used. SMOH does not provide information regarding any method(s) used to validate their guidelines.		

SOURCE(S) OF FUNDING Abbreviations Back to TOC	
GOLD (2009)	Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Dey, Forest Laboratories, Inc, GlaxoSmithKline, Novartis, Nycomed, Philips Respironics, Pfizer, Schering-Plough
SMOH (2006)	Singapore Ministry of Health
VA/DoD (2007)	United States Government

BENEFITS AND HARMS Abbreviations Back to TOC	
Benefits	
GOLD (2009)	Appropriate diagnosis, management, and prevention of COPD
SMOH (2006)	Appropriate diagnosis and management of patients with COPD
VA/DoD (2007)	Appropriate management of outpatient COPD
Harms	
GOLD (2009)	• **Arterial Blood Gas Measurement**: Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising. • **Beta$_2$-agonists**: Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting beta$_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD. • **Anticholinergics**: Anticholinergic drugs are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires

	further investigation. Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by these drugs, and respiratory infection rates are not increased. • **Methylxanthines**: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). • **Oral Glucocorticosteroids**: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. • **Invasive Mechanical Ventilation**: Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.
SMOH (2006)	• Side effects of medication • Risk of fire and explosion when using oxygen therapy. Patients requiring oxygen therapy should be advised against smoking cigarettes.
VA/DoD (2007)	Side effects of pharmacotherapy (see Table C6 in the original guideline document for cautions and special instruction for selected COPD drug therapy)

CONTRAINDICATIONS **Abbreviations** **Back to TOC**	
GOLD (2009)	• **Beta-Blockers**: Beta-blockers commonly prescribed for heart disease are usually contraindicated in COPD.

	• **Noninvasive Intermittent Ventilation** Relative Contraindications for Noninvasive Intermittent Ventilation (NIV): • Respiratory arrest • Cardiovascular instability (hypotension, arrhythmias, myocardial infarction) • Change in mental status; uncooperative patient • High aspiration risk • Viscous or copious secretions • Recent facial or gastroesophageal surgery • Craniofacial trauma • Fixed nasopharyngeal abnormalities • Burns • Extreme obesity
SMOH (2006)	Contraindications to specific surgeries (bullectomy, lung volume reduction surgery [LVRS]) and lung transplantation are listed in the original guideline document.
VA/DoD (2007)	**Short-acting Bronchodilators** The use of beta$_2$-agonists is contraindicated in patients with unstable arrhythmia or angina.

Abbreviations
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CHF, congestive heart failure

COPD, chronic obstructive pulmonary disease

ECG, electrocardiogram

ED, emergency department

FEV_1, forced expiratory volume in one second

GOLD, Global Initiative for Chronic Obstructive Lung Disease

ICU, intensive care unit

LTOT, long-term oxygen therapy

NIV, noninvasive ventilation

PEF, peak expiratory flow

SMOH, Singapore Ministry of Health

SMX, sulfamethoxazole

TMP, trimethoprim

VA/DoD, Department of Veterans Affairs, Department of Defense

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This synthesis was prepared by ECRI on October 8, 2001. It was reviewed by the guideline developers as of November 15, 2001. It was updated to include NCCCC/NICE and FMS and updated GOLD recommendations on March 24, 2005. The information was verified by NICE on May 3, 2005. This synthesis was updated on October 20, 2005 to reflect updated GOLD guidelines. This synthesis was updated on April 19, 2006 to reflect revised FMS guidelines. This synthesis was updated on December 18, 2006 to withdraw guidelines from ACP/ACCP which were archived due to their age. This synthesis was updated most recently on June 3, 2008 to update GOLD recommendations. This synthesis was revised in June 2009 to update GOLD recommendations and remove FMS recommendations and again in February 2010 to remove NICE recommendations and add VA/DoD recommendations. The information was verified by VA/DoD on April 6, 2010. The synthesis was revised most recently in April 2010 to update GOLD recommendations.

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